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Autoimmune hepatitis *vs.* Pregnancy

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Summary

Introduction

Autoimmune hepatitis (AIH) is a disease of unknown etiology. In pregnancy, it may have mild clinical course as well as can lead to liver failure, or exacerbation of clinical symptoms. In pregnant women the severity of symptoms is often observed between the second and third trimester, and in the puerperium. The disease is marked by enhanced activity of Th lymphocytes, which hepatocytes recognize as foreign antigens. This results in interleukin production activating B lymphocytes, and the production of specific antibodies attacking and destroying the hepatocytes.

Case report

A 35-year old patient, CII PII, 7 Hbd, with autoimmune hepatitis reported for a check-up. Her first pregnancy was 18 years ago, without history of underlying disease, carried to term without complications. The woman gave birth to a baby-son weighing 3,280g, 10 points Apgar. The delivery was spontaneous and uneventful. The patient got pregnant after an 18-year break. When she twice-tested positively for pregnancy, the treatment with azathioprine was switched to prednisolone.

Over the pregnancy the patient was hospitalized 4 times, in 25, 29, 35, and 37 week of gestation due to a threat of preterm delivery, and pregnancy-related cholestasis associated with AIH.

In 37 week of gestation, delivery was induced, and she gave birth to a healthy male, weighing 2,650 g, body height of 49 cm, 10 points Apgar scale. The liver function improved and stabilized after the delivery. Treatment with prednisolone has been continued, and the patient's condition is still controlled.

Pregnant patients with autoimmune hepatitis often experience exacerbation of the disease, especially in the third trimester, and in the postpartum period. This case shows that with proper care it is possible to continue and terminate pregnancy safely for the mother and her newly born baby.

Key words: autoimmune hepatitis, pregnancy, liver cirrhosis

Introduction

Autoimmune hepatitis (AIH) is a chronic disease of unknown etiology, with an incidence of 11-17 per 100,000 cases [3.6]. Approximately 70% of the patients are women. Clinical manifestations depend on the dynamics of inflammatory process. In the course of disease, Th lymphocytes are activated, and hepatocytes recognize them as foreign antigens. Th lymphocytes produce interleukins that activate B lymphocytes to produce specific antibodies that attack and damage the hepatocytes. As B lymphocytes increase, hypergammaglobulinemia develops, which can lead to acute or chronic hepatitis [9,14]. Patients have abnormal laboratory results, and develop clinical symptoms such as fatigue, weakness, drowsiness, abdominal pains, sometimes anorexia [14,19].

In the literature, there are over 200 pregnancies reported in women suffering from AIH [1]. In case of women suffering from AIH, pregnancy poses a problem for both the pregnant and the developing fetus. Complications occur in 21% pregnant women, and in 90% women after termination of pregnancy [5,10,18,21]. The risk of miscarriage increases to 24%, and of preterm delivery to 17% [4]. In women with AIH, the severity of liver disease and its biochemical parameters are often exacerbated [26]. Impaired hormonal metabolism due to glycocorticosteroid treatment can result in menstrual disorders and eventually infertility in women. [13,14]. Most young patients respond positively to standard treatment.

Case report

In 2016 a 35-year old patient with a positive pregnancy test was seen in the gynecological office to confirm pregnancy. Her past history revealed autoimmune hepatitis diagnosed in 2008. The patient was treated with azathioprine and prednisone. The patient was not qualified for liver transplantation as her biochemical parameters of liver tests were normal.

Eighteen years earlier she gave birth in 38 Hbd. to a male, weighing 3,280g / 10 points Apgar scale, uneventful spontaneous delivery.

USG scan taken in 7 Hbd.: CRL-12 mm, single embryo, live, visualized in the uterine cavity. Gall bladder normal, no signs of chorionic detachment. Pharmacological treatment was modified by a specialist in infectious diseases, prednisone was started instead of azathioprine.

Throughout the pregnancy, the patient was monitored by a specialist in infectious diseases, obstetrician and gynecologist.

The patient was hospitalized four times in the Department of Pregnancy Pathology in 25, 29, 35 and 37 Hbd. for autoimmune hepatitis, pregnancy-associated cholestasis, and threatening preterm delivery.

The patient was first hospitalized in the 25th week of gestation. She reported at the Clinic of Pregnancy Pathology for skin pruritus and abdominal pain. USG scan found no abnormalities, fetal biometry was normal for the gestational age, laboratory tests found no significant deterioration in the liver function parameters. After a 3-day stay in hospital, the pregnant woman was discharged home. She was prescribed Prednisone, Ursopol, Hepa Merz, and Essentiale Forte.

In the 29th week of pregnancy, the patient was again hospitalized for intense cholestasis in the form of generalized skin itching, and threatening premature labor. The patient was given Hydroxyzine, orally, and Lutein vaginally. USG scan showed no abnormalities in the fetal development. Cardiotocography was normal. Laboratory test found worsened parameters of the liver function, concentrations of aminotransferases and bile acids were increased. After a five-day hospitalization, the pregnant woman (fetus live) was discharged home.

Another hospitalization was in the 35th week of gestation: more than doubled aminotransferase concentrations, and increased bile acid concentrations up to 35 umol / l (lab tests taken by the patient). During a three-day hospitalization on the ward, the parameters normalized. The patient was discharged home with live pregnancy, USG and cardiotocography normal.

During the entire duration of pregnancy, periodic deterioration in the liver function parameters was observed in laboratory tests. (Table 1).

Table 1. Liver function parameters observed over the pregnancy

Biochemical paremeters	Gestation age			
	Normal range	25Hbd	29Hbd	35Hbd
ALP	35-125 U/L	164 U/L		

ALT	5-50 U/L	101 U/L	136 U/L	104 U/L
AST	5-50 U/L	52 U/L	70 U/L	58 U/L
Total protein	6.0-8.0 g/dl	6.40 g/dl	6.7 g/dl	7.0 g/dl
Bilirubin	0.10-1.30 mg/dl	0.40 mg/dl	0.47 mg/dl	0.63 mg/dl
CRP	0.1-5.0 mg/l	2.19 mg/l		
APTT	26.0-40.0 sek	24.5 sek	23.1 sek	22.4 sek
PT	9.7-14.5 sek	10.5 sek	10.3 sek	9.8 sek
INR PT	70-130 %	109 %	104 %	110 %
INR	0.8-1.2	0.9	0.9	0.8
TT	15.0-25.0 sek	15.0 sek	14.6 sek	15.3 sek
GGTP	10-40 U/L	50 U/L	42 U/L	
Glucose	65-100 mg/dl	71 mg/dl		
Creatinine	0.70-1.30 mg/dl	0.70 mg/dl	0.71 mg/dl	0.69 mg/dl
Urea	20-45mg/dl	18 mg/dl		25 mg/dl
Uric acid	3.40-7.00mg/dl	4.40 mg/dl	4.6 mg/dl	5.8 mg/dl
Bile acids	0-15.0 umol/l	10.9 umol/l	34.4 umol/l	29.6 umol/l
LDH	120-230 U/L	187 U/L	171 U/L	190 U/L
Urinanalysis	NAD	NAD	NAD	NAD

HGB	12.0-15.6 g/dl	13.0 g/dl	13.1 g/dl	14.8 g/dl
HCT	35.0-46.0 %	37.6 %	37.8 %	42.3 %
RBC	3.6-5.2 M/ul	4.13 M/ul	4.13 M/ul	4.68 M/ul
WBC	4.1-10.9 K/ul	7.35 K/ul	9.9 K/ul	9.88 K/ul
PLT	140-440 K/ul	164 K/ul	170 K/ul	196 K/ul
Na	137-146mEq/l	134 mEq/l	138 mEq/l	137 mEq/l
K	3.5-5.2 mEq/l	3.8 mEq/l	3.8 mEq/l	4.2 mEq/l

In the 37th week of gestation, the patient was admitted to the ward to terminate her pregnancy. On admission she presented with intense skin pruritus and slow fetal movements, liver parameters deteriorated. The patient was transferred to the delivery room, Mizodel vaginal pessary was inserted to induce labor. When the labor commenced, at 4-cm cervix dilation, epidural anesthesia was administered. The patient delivered naturally, a healthy newborn male was born, 2,650 g, 49 cm, Apgar score of 10 points in the first, third and fifth minute, umbilical cord blood pH 7.419. The postpartum period uneventful. The patient was discharged home on 7 day.

Currently, the patient is followed-up in the Clinic of Infectious Diseases, and Prednisone continued. There has been no evidence of relapse of AIH symptoms. Since the liver function stabilized, the patient does not require liver transplantation.

Discussion

Diagnosis of autoimmune hepatitis is not easy, and there is no a single diagnostic test to confirm the disease. Increased values of sMA, ANA, anti-LKM-1, anti-sLA, Lp, p-ANCA, anti-LC1, anti-AsGpR, and hypergammaglobulinemia are the most common parameters that may indicate the condition [15, 17, 18].

There are three types of autoimmune hepatitis distinguished on the basis of the presence of serum antibodies [16, 23]:

• type 1 – positive AsMA (anti-smooth muscle antibody) or ANA (anti-nuclear antibody),

• type 2 – positive anti-LKM-1 (anti-liver kidney microsomes) ,

• type 3 – positive anti-sLA (anti-soluble liver antibody), or antibodies that react with hepatic and pancreatic antigens (Lp).

Differential diagnosis should exclude other metabolic and viral hepatitis [6,17,20]. Autoimmune hepatitis is diagnosed on the basis of the criteria established by the International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis [7,11,22]. Diagnostic imaging uses ultrasound and CT scan. Liver biopsy is also performed, but it is not a pathognomonic study. The image does not differentiate AIH from chronic hepatitis [22].

The recommended treatment uses corticosteroids (Prednisone) at a dose of 40-60 mg or 1 mg / kg inducing remission of the symptoms [12,24,28].

In the world literature, about 200 cases of pregnancy were reported in women with AIH, - some complicated by cirrhosis [1]. According to the literature, 20% pregnant women suffering from AIH experience exacerbated symptoms at various periods of their pregnancies. In the postpartum period and laying-in complications are observed in 90% cases [5,10,15,18]. Complications may cause decompensation of the liver function, the need for liver transplantation, or death of the patient [17]. Fortunately, most women are controlled and immunosuppressed.

In a study by Westbrook et al., 81 pregnant women with AIH were examined. Hepatic cirrhosis in the mother was associated with a higher risk of serious complications (death, transplantation within up to 12 months after pregnancy, or liver decompensation within up to 3 months after pregnancy). In the above presented case, a temporary deterioration of the liver function during pregnancy with later stabilization of the function was observed.

The remission of autoimmune hepatitis during pregnancy was described several times in the literature [5]. It is currently believed to be due to increased levels of estrogens that inhibit the immune activity, and progesterone which affects the anti-inflammatory properties of Th2 helper lymphocytes [25,27]. Immune mechanisms developing during pregnancy also include increased number of T regulatory lymphocytes responsible for the immune tolerance of the fetus [2,3].

Unfortunately, after the termination of pregnancy those mechanisms disappear, which is why AIH exacerbation is observed afterwards. In the above presented case, permanent deterioration in the liver function was not observed during or after the completion of both pregnancies, and over several years of follow-up period.

Another important problem raised in the literature is the effect of pregnancy on portal hypertension [8.20]. Because of altered visceral flow and anatomical conditions in the abdomen associated with the growing uterus, the risk of esophageal varices is significantly increased [8, 20].

According to literature data, the percentage of live births among pregnant women with AIH is 71-86% [5,10,15,23], and preterm births occur in up to 20% cases [17]. In a study by Westbrook et al., pre-pregnancy liver cirrhosis in the mother was associated with a statistically lower live birth rate and a higher rate of prematurity than in AIH women without

advanced cirrhosis. Neonates of the mothers with cirrhosis or exacerbated symptoms in pregnancy also required statistically more frequent admission to neonatal intensive care units.

In the afore mentioned case, both pregnancies resulted in the birth of two healthy newborn males (in 37 and 38 Hbd). The babies were born with normal birth weight, none of them required intensive neonatal care.

The presented case shows that a successful outcome can be expected for both the mother and the fetus provided pregnant women with impaired liver function in the course of AIH receive proper gynecological, obstetric and hepatological care. Improvement and stabilization of the liver function were observed after pregnancy and persisted over a 10-year follow-up period. Currently they allow for conservative treatment of the patient who does not require liver transplantation today.

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